Remarks

Claims 3, 5, 11, 17, 28, and 32-33 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Totten et al. (GB 2,202,145) in view of Jacobs et al. (US 5,939,085) and Sang et al. (US 6,143,310). Summaries of these references have previously been provided in, for example, Applicant's responsive submission of June 24, 2004.

The Examiner asserts that the compositions of the cited art inherently exhibit the same properties as do the presently claimed compositions. Applicant respectfully submits that the effectiveness property known of Totten et al. '145 is failure, while the effectiveness property of the presently claimed compositions is success. Applicant further respectfully submits that no motivation exists in the cited art for combining the references in order to change the effectiveness property of Totten et al. '145 from failure to success in the topical treatment of skin maladies. Moreover, Applicant respectfully submits that no teaching of the presently claimed component concentrations is found in the cited prior art, whether taken alone or in combination.

The Examiner has maintained the position that the presently claimed compositions do not provide a result that is unexpected over that demonstrated in the cited prior art. In order to more fully complete the record, and to further establish the clearly unexpected results generated by the claimed compositions, Applicant encloses herewith a Declaration under 37 CFR § 1.132. The enclosed Declaration has further been submitted in order to address the specific points raised by the Examiner in the Official Action dated July 28, 2004.

In particular, the enclosed Declaration specifically and directly compares the data generated in experiments utilizing the compositions of the present invention to data generated in experiments utilizing the composition of Totten et al. '145. The data generated by Van Beaver et al., reporting the effectiveness of the compositions described in Totten et al. '145, support a conclusion that the composition of Totten et al. '145 has no advantage over placebo. By contrast, the data generated through the experimental use of the compositions of the present invention indicate that such compositions are indeed effective against skin maladies. The enclosed report further provides statistical evidence that the difference seen in a direct comparison between compositions of the

present invention and that described in Totten et al. '145 is both statistically and practically significant. The successful treatment of the vast majority of patients receiving topical treatment with the compositions of the present invention demonstrates that the unexpected benefits associated with the claimed compositions constitute clear and convincing evidence of this unexpected result.

In the Official Action of July 28, 2004, the Examiner directs Applicant's attention to MPEP §§716.02(a)-(g) for the guidelines in showing unexpected results. A Board of Patent Appeals and Interferences opinion cited in MPEP §716.02(a) states that evidence of unexpected superior therapeutic activity of a claimed compound against anaerobic bacteria is sufficient to rebut prima facie obviousness, even without evidence that the compound is effective against all bacteria where the compound is broadly recited in the claim as being an antibiotic, Ex Parte A, 17 U.S.P.Q.2d 1716 (Bd. Of Pat. App. & Inter. 1990). The unexpected superior therapeutic activity cited in Ex Parte A, therefore, constitutes a sufficient demonstration of unexpected results to itself overcome a prima facie rejection of obviousness under 35 USC §103(a). The facts present in this case appear to be on point with Ex Parte A, with the submitted data and declarant

statements clearly demonstrating an unexpectedly superior therapeutic activity of the claimed compositions over that shown by the composition of Totten et al. '145. It correspondingly follows that Applicant's submissions overcome the obviousness rejections put forward by the examiner.

In addition to the above, the enclosed Declaration specifically attests to the fact that the compositional components recited in independent claim 32 represent the components responsible for the unexpected results demonstrated in the experimental findings. In other words, the results indicated through the use of the "Altoderm" formulation is represented by pending claim 32, such that the results of the Declaration are indeed commensurate in scope with the pending claims.

The enclosed Declaration further specifically points out that, while the newly submitted data is linked to the effective treatment of atopic dermatitis, those of ordinary skill in the art would readily recognize that the presently claimed compositions would also be effective against a vast array of other skin disorders. Accordingly, pending claim 32 as well as all claims dependent therefrom, are indeed commensurate in scope with the Declarations filed by the Applicant.

For the foregoing reasons, the claims as currently pending are believed to be unobvious and patentable over the cited prior art, and particularly over Totten et al. '145 in view of Jacobs et al. '085 and Sang et al. '310. The claim rejections based thereon should accordingly be withdrawn.

Claim 9 stands rejected under 35 USC §103(a) as being unpatentable over Totten et al. '145 in view of Jacobs et al. '085 and Sang et al. '310, and further in view of Dener et al. (WO98/04537) and Haider (1979). The references of Dener et al. '537 and Haider, whether taken alone or in combination, fail to cure the defects of the cited references discussed above. Therefore, the claim rejections based thereon should be withdrawn.

Claim 12 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Totten et al. '145 in view of Jacobs et al. '085 and Sang et al. '310, and further in view of the Handbook of Cosmetic Science and Technology. These references, whether taken alone or in combination, fail to cure the defects of Totten et al. '145, Jacobs et al. '185, and Sang et al. '310. The claim rejections based thereon should accordingly be withdrawn.

For the foregoing reasons, the currently pending claims are believed to be unobvious and patentable over the

cited prior art, whether taken alone or in combination. Applicant therefore submits that the pending claims are allowable on the merits. An early allowance is respectfully solicited.

Respectfully submitted,

HAUGEN LAW FIRM PLLP

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CLINICAL STUDY REPORT

A randomised, multi-centre, double-blind, placebo-controlled, parallel-group comparative trial to evaluate the efficacy, safety and acceptability of a topically applied lotion of sodium cromoglicate (Altoderm®) in the treatment of atopic dermatitis in children.

Name of test drug:	Sodium cromoglicate
Indication studied:	Atopic dermatitis
Name of the sponsor:	Hewlett Healthcare Ltd
Protocol identification:	HH.SKINP.01
Development phase of study:	III
Study initiation date:	June 2002
Date of early study termination:	N/A
Study completion date:	August 2003

Sponsor's responsible medical officer:

Dr Alan M Edwards.
Medical Director,
Vectis Allergy Ltd.
Hanover House,
Brook,
Newport,
Isle of Wight.
PO30 4HG.

Name of sponsor signatory:

AJ Wigmore,
Hewlett Healthcare Ltd.
27 Granby Street
Loughborough
Leicestershire
LE11 3DU.

This study was performed in compliance with Good Clinical Practice (GCP)

SYNOPSIS

Name of Sponsor/Company: Hewlett Healthcare Ltd.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Altoderm	Volume:	
Name of Active Ingredient: Sodium cromoglicate	Page:	

Title of Study:

A randomised, multi-centre, double-blind, placebo-controlled, parallel-group comparative trial to evaluate the efficacy, safety and acceptability of a topically applied lotion of sodium cromoglicate (Altoderm®) in the treatment of atopic dermatitis in children.

Investigators: Dr S. H Arshad, Dr K D Foote, Dr J Robinson, Dr I Pollock.

Study centres: Four study centres, all in the United Kingdom

Publication (reference):

None (manuscript in preparation for publication)

Studied period (years):	2002 - 2003	**Phase of development:** III
Date of first enrolment:	June 2002	
Date last patient completed:	August 2003	

Objectives:

To compare the efficacy/safety/acceptability of Altoderm versus a placebo control in the treatment of atopic dermatitis in children.

Methodology:

A randomised, double-blind, parallel-group, placebo-controlled study. Study design incorporated a two week baseline period after initial patient screening, followed by a 12 week treatment period.

Number of patients (planned and analysed):

Planned: 120

Randomised: 118 patients
4 patients randomised but no on-treatment data provided, giving:
Altoderm: 58 patients
Placebo: 56 patients

Analysed:
Safety population: 114 patients
Altoderm: 58 patients
Placebo: 56 patients
ITT population: 114 patients
Altoderm: 58 patients
Placebo: 56 patients

No PP population was defined.

Name of Sponsor/Company: Hewlett Healthcare Ltd.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Altoderm	Volume:	
Name of Active Ingredient: Sodium cromoglicate	Page:	

Diagnosis and main criteria for inclusion:
Children of either sex between 2 and 12 years of age, with atopic dermatitis according to recognised diagnostic criteria and a score of ≥25 and ≤60 using the SCORAD scoring system for atopic dermatitis.

Test product:	Altoderm (4%w/w sodium cromoglicate in a cutaneous emulsion formulation)
Dose:	applied liberally twice daily to affected area(s) of skin
Mode of administration:	cutaneous application
Batch numbers:	DEV 1650 A, DEV 1651 A, DEV 1682 A, DEV 1687 A, DEV 1702 A
Duration of treatment:	12 weeks

Reference product:	Placebo (Altoderm formulation without sodium cromoglicate ie vehicle only)
Dose:	applied liberally twice daily to affected area(s) of skin
Mode of administration:	cutaneous application
Batch numbers:	DEV 1650 P, DEV 1651 P, DEV 1682 P, DEV 1687 P, DEV 1702 P
Duration of treatment:	12 weeks

Criteria for evaluation:

Efficacy:
Primary criterion:
Change in SCORAD score for atopic dermatitis over treatment period from baseline measurement (prior to start of treatment)

Secondary criteria:
- Change in severity of symptoms of atopic dermatitis (overall skin condition, itching, sleep loss) over treatment period from baseline measurements, as recorded daily on weekly diary cards (by patient's parent) using a numerical scoring scale (0-3)
- Change in usage (number of days and frequency per day) of concomitant topical corticosteroid preparations over treatment period from baseline measurements (recorded on diary cards by patient's parent)
- Patient's parent and investigator opinions of effectiveness of treatment (at end of treatment period/withdrawal as appropriate)
- Patient's parent opinion of acceptability of treatment (at end of treatment period/withdrawal as appropriate)

Safety:
Adverse events reported during treatment period

Statistical methods:
Changes from baseline values for SCORAD scores, diary card symptom scores and topical corticosteroid usage between Altoderm and placebo-control treatment groups were analysed using a two-way Analysis of Variance (ANOVA) model with the factors treatment and centre (significance level 5%). Global opinions of effectiveness and acceptability were compared between the treatment groups using this model. 95% confidence intervals for the differences between treatment groups were calculated. Values were imputed for withdrawn patients for SCORAD score and diary card symptom scores according to a last observation carried forward method.

Opinions of effectiveness were also presented as a dichotomy of those patients for whom the opinion was very/moderately effective, and those for whom it was slightly effective/no effect/made condition worse. These were analysed using Cochran-Mantel-Haenszel test adjusting for centre.

The residuals from the variance model were checked for homogeneity and normality.

Name of Sponsor/Company: Hewlett Healthcare Ltd.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Altoderm	Volume:	
Name of Active Ingredient: Sodium cromoglicate	Page:	

Summary:

Efficacy results:
Primary efficacy variable

At the end of the treatment period, a statistically significant difference was seen between the Altoderm and placebo-control groups in mean reduction in SCORAD total score from baseline. The mean reduction in SCORAD score was -13.2 for Altoderm and -7.6 for placebo (least square means), giving a difference between treatments of -5.6 (95% confidence interval: -10.3, -1.0) in favour of Altoderm ($p=0.018$). A statistically significant difference ($p<0.05$) between treatments in favour of Altoderm was also noted at the second and third of three assessments during the treatment period.

Secondary efficacy variables

Reductions in diary card symptom scores (for overall skin condition, itching, sleep loss) and a derived parameter (mean of the three symptom scores) were seen in both Altoderm and placebo-control groups, but the improvement was more pronounced with Altoderm. The difference between treatments for mean reduction in mean symptom score and overall skin condition was -0.16 ($p=0.068$) (-0.20, $p=0.017$ with outlier value excluded) and -0.23 ($p=0.020$) respectively in favour of Altoderm.

Concomitant usage of topical corticosteroids decreased in both treatment groups, however the reduction was greater with Altoderm. The difference between treatments was -0.26 in favour of Altoderm ($p=0.044$) for mean reduction in frequency of uses per day, and -0.12 in favour of Altoderm ($p=0.053$) for mean reduction in proportion of days used.

Favourable opinions of treatment effectiveness were given by parents and investigators for both treatments, with more than 50% being 'moderately effective' or 'very effective' in both treatment groups. There was no statistically significant difference in either parent or investigator opinions between treatment groups. Study medication was rated as 'acceptable' by 84.5% of parents for patients in the Altoderm treatment group, and by 87.5% of parents for patients in the placebo-control group.

Safety results:

Treatment-emergent adverse events were reported by 32 patients from the Altoderm treatment group (55.2%) and 34 patients from the placebo-control group (60.7%). The largest number of patients reporting adverse events was recorded for the infections & infestations System Organ Class (Altoderm, 15 patients reporting; placebo, 18 patients reporting) and the respiratory, thoracic & mediastinal disorders System Organ Class (Altoderm, 18 patients reporting; placebo, 15 patients reporting). Of the adverse events reported, many (nasopharyngitis, infected eczema, upper respiratory tract infection) were not unexpected in the paediatric population studied. No treatment-emergent adverse events were rated as 'very severe'.

Treatment-emergent treatment-related adverse events were reported by seven patients (12.1%) from the Altoderm treatment group and four patients (7.1%) from the placebo-control group. The majority of these events concerned cutaneous disorders (erythema, pruritus) and application site reaction (burning); suggestive of local irritation on application of study medication. No treatment-emergent treatment-related events were rated as 'severe' or 'very severe'.

No deaths occurred during this study. Five serious adverse events were recorded, none of which were considered possibly or probably related to study medication. Study treatment was withdrawn from ten patients owing to adverse events, eight from the Altoderm treatment group and two from the placebo-control group. In six cases the relationship to study medication was deemed possibly, probably or highly probably related to study medication (Altoderm, five patients; placebo, one patient). In the majority of cases the event reported [illegible].

Name of Sponsor/Company: Hewlett Healthcare Ltd.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Altoderm	Volume:	
Name of Active Ingredient: Sodium cromoglicate	Page:	
Conclusions: Altoderm represents an effective, safe and acceptable treatment for atopic dermatitis in children. A stronger than expected placebo effect was noted, possibly due to the emollient properties of the placebo used. Altoderm may cause mild or moderate local irritation at the site of application in some patients.		
Date of report: April 2004		

Attorney Docket 2000-0702/ORI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re App: Brian Hawtin Art Unit: 1619
Serial No: 09/701,140 Exam: Lauren Q Wells
Filed: November 21, 2000
For: Formulation

DECLARATION OF ALAN EDWARDS

The Commissioner of Patents and Trademarks

Washington, D.C. 20231

Sir:

I, Alan Edwards, hereby declare as follows:

1. That I am a citizen of the United Kingdom, and a resident of Newport, Isle of Wight, UK, residing at Hanover House, Brook, and involved in the clinical evaluation of the invention described in the above-identified application for United States Letters Patent;

2. That I am presently employed by Vectis Allergy Limited where I hold the title of Medical Director, a position which I have held for 8 years, it being in the business of consultancy services to the pharmaceutical industry. Prior to that I was employed by Fisons Plc from 1974 to 1995.

3. That I have been engaged in the development and assessment of pharmaceutical compositions for the treatment of skin-related diseases and conditions for a period of at least about 22 years. Specifically, I have been engaged in the development and assessment of pharmaceutical compositions comprising sodium cromoglycate and related compounds, in relation to both skin-related diseases and conditions, and other diseases and conditions for 28 years. The compositions on which I have worked include compositions for injection, oral ingestion and inhalation as well as for topical administration. A copy of my *Curriculum vitae* was supplied with an earlier Declaration;

4. That in the course of these activities, I have personally become familiar with the problems encountered with transdermal transmission of pharmaceutically active drugs in topical treatments, and with the evaluation of such drugs in clinical trials;

5. That in the course of the prosecution of the above-identified application for United States Letter Patent, I have become familiar with the subject matter of the references cited by the examiner in the course of prosecution, including the following:

British Patent No 2 202 145
European Patent Application No 0 189 861 A2
PCT Publication No. 98/04537
US Patent No 5,888,478
US Patent No 5,190,917
US Patent No 4,883,792
US Patent No 5,939,085
US Patent No 6,143,310
Haider
Handbook of Cosmetic Science and Technology

and, have related the substance of the claimed subject matter to disclosures of these references;

6. That the subject matter of these references do not provide the unexpected benefit of the presently claimed compositions, with the reasons being as follows:

The examiner has not indicated why the material presented in my Declaration is not considered to show that the composition of Totten et al (British Patent No. 2,202,145) does not exhibit the same properties as the presently-claimed composition. My Declaration filed 29 September 2003 stated and shows that the clinical trial reported in Van Bever & Stevens Eur J Pediatr 1989;149:74 was, in fact, a trial of the formulation described in the application by Totten et al. This trial, as well as other unreported clinical trials, showed that the formulation described in the application by Totten et al. had no beneficial effect.

For example:

"*In conclusion, 4% nedocromil sodium cream, applied during 4 weeks, twice daily* ***has no advantage over placebo*** *in the treatment of patients (older children and adults) with atopic dermatitis*" (final paragraph of Results section of Van Bever et al.)(emphasis added).

In contrast to the failure of the composition described in Totten et al., and reported by Van Bever et al., the present formulation has been used with benefit by patients, as I set out in my previous Declarations. In addition to the data presented in my previous Declarations, I have attached a report of a clinical trial carried out on a formulation having acting components as defined in the present claims, and being utilized in the treatment of eczema and/or atopic dermatitis. The results achieved with the present formulation are vastly superior to those achieved with the Totten *et al* formulation, as stated in Van Bever et al.

The presently attached study shows that the formulation having acting components as defined in the present claims has a statistically significant beneficial effect when compared with either the treatment that patients were previously receiving or with placebo.

For example, page 4 of the attached report states:

> *"At the end of the treatment period, a statistically significant difference was seen between the Altoderm and placebo-control groups in mean reduction SCORAD total score from baseline. The mean reduction in SCORAD score was -13.2 for Altoderm and -7.6 for placebo (least square means), giving a difference between treatments of -5.6 (95% confidence interval: -10.3, -1.0) in favour of Altoderm (p=0.018). A statistically significant difference (p<0.05) between treatments in favour of Altoderm was also noted at the second and third of three assessments during the treatment period."*

The attached report further states at page 5, in the section entitled "Conclusions", that:

> *"Altoderm represents an effective, safe, and acceptable treatment for atopic dermatitis in children."*

In addition, the results reported in Exhibit A of my Declaration filed on 29 September 2003, indicate that 87.5% of the 40 patients involved in the original study having atopic dermatitis or eczema showed improvement upon treatment with the claimed topical composition. Such improvement was noted where previous treatments using conventional methodologies had failed.

Clearly, the formulation as defined in the present claims is having a practical benefit for patients which is statistically significant. Contrast this with the utter lack of benefit seen with the formulation of Totten et al in the trial and corresponding data reported in Van Bever and Stevens.

In light of the above, it appears to me unreasonable and inappropriate to conduct further testing of the formulation described in the application by Totten et al when there are already published results which show that the formulation described in the application by Totten et al is ineffective as a treatment for a skin condition. Indeed, in view of the known lack of efficacy of the Totten et al formulation it would be unethical to treat patients with this formulation and therefore to carry out a trial of the form that the examiner appears to be requiring.

In addition, the trials conducted have revealed that it is the combination of the amphoteric surfactant and the alkoxylated cetyl alcohol component that make the difference between an aqueous and oil phase formulation that is effective in transdermally delivering the polar drug and one that is not. The skilled person would appreciate, for example in view of previous trials using cromoglycate-containing formulations, that it is the presence of the amphoteric surfactant and the alkoxylated cetyl alcohol that is responsible for the improvement in results seen with the formulation tested in the

present trials. Indeed, it is the presence of the amphoteric surfactant and the alkoxylated cetyl alcohol in their respective concentrations that provide the beneficial activity identified in the trial results, and specifically not the presence of the remaining components making up the Altoderm skin lotion. The remaining Altoderm components, such as those listed in pending claim 13, are present in the Altoderm product simply to provide a stable topical substance for application onto a patient's skin. It is evident to those of ordinary skill in the art that a vast array of additive components may be utilized in combination with the acting ingredients of the amphoteric surfactant, alkoxylated cetyl alcohol, and polar drug, while maintaining the efficacy of the claimed composition. In other words, though the Altoderm product utilized in the above-referenced trials contains ingredients in addition to the presently claimed amphoteric surfactant, alkoxylated cetyl alcohol, and polar drug, such additional ingredients are not critical to the efficacy (transdermal transmission) of the polar drug in the topical treatment of skin disorders. Accordingly, the claims as now pending are indeed commensurate in scope with the results obtained in the clinical trial in that only the claimed components, and their associated concentrations, meaningfully contribute to the operation of the Altoderm formulation utilized in the clinical trials.

Although the clinical trials were directed to patients suffering from eczema and/or atopic dermatitis, the claimed composition is also expected to be effective against a variety of other skin disorders such as, for example, the disorders listed in claim 17 ie contact sensitivity, psoriasis, drug sensitivity reactions, apthous ulcers, Behcet's syndrome, pemphigus, urticaria, urticaria pigmentosa, pyroderma gangrenosum, chronic skin ulcers, ulcers associated with Crohn's disease, burns, insect stings/bites, herpetic inferctions, systemic sclerosis, morphoea, dermal nodular fibrosis and sunburn. It is therefore inappropriate to restrict the pending claims to a particular skin condition wherein the formulation provides improved transdermal delivery of a polar drug so as to enable a significantly wider treatment relevance.

7. That based upon my education and experience, I am fully confident that the Totten *et al* reference (GB 2 202 145) reference, the Motoaki *et al* (EP 0 189 861) reference, the Maurin (US 5,888,478) reference, the Sang *et al* (US 6,143,310) reference, the Jacobs *et al* (US 5,939,085) reference, the Dener (WO 98/04537) reference, the Haider reference, and the Handbook of Cosmetic Science and Technology reference, whether taken alone or in combination, fail to teach or suggest the unexpected beneficial results of the pharmaceutical compositions embodied in the presently pending claims;

8. That this Declaration is given for the purpose of defining and delineating distinctions present in the claimed subject matter of this application from the disclosures available in the references being relied upon by examiner, and that this Declaration is given in support of the patentability of the claims presently under consideration.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on 23 September, 2004

Alan M Edwards. MB BChir